REMARKS

The Examiner withdrew claims 51-67. Claims 1-50 and 68 are pending. These amendments add no new matter. Claims 1-50 and 68 are under consideration.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 10 and 26-50 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter. Office Action, page 2, section 2.

The Examiner rejects claims 10 and 35 as allegedly vague and indefinite "because it is still unclear whether or not the nucleic acid from the virus or prokaryote as listed in the claims is chemically modified." Office Action, page 2, section 2a. The Examiner requested clarification. *Id.*

In short, the nucleic acid derived from a virus or prokaryote as in claims 10 and 35 may or may not be chemically modified. "During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification." Manual of Patent Examining Procedure (MPEP) §2173.05(a). Thus, the methods of claims 10 and 35 include embodiments where the nucleic acids from the sample are chemically modified. To answer the Examiner's question, the nucleic acid referred to in claims 10 and 35 may be chemically modified or may not be chemically modified. Both chemically modified nucleic acids and non-modified nucleic acids are within the scope of claims 10 and 35. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejects claims 26-50 under 35 U.S.C. §112, second paragraph, as allegedly vague and indefinite. Office Action, page 2, section 2b. Specifically, the Examiner alleges that "it is still unclear how the sequence of the at least one

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

amplification product of the first reaction composition is determined since the first reaction composition does not has a fluorescent indicator." Office Action, page 2, section 2b.

The sequence of the at least one amplification product of the first reaction composition may be determined by, as a non-limiting example that does not use a fluorescent indicator, a Sanger dideoxynucleotide reaction using a radioactive isotope. Methods of determining the sequence of nucleic acids without the use of fluorescent indicators have existed for several decades, and are not new to the art. For example, chain termination sequencing without fluorescent indicators is widely known and used in the art. *See* Sanger, et al., 1977, "DNA Sequencing with Chain-Terminating Inhibitors," *Proc. Nat Acad. Sci.* 74:5463-5467; and Sambrook et al., Molecular Cloning: A Laboratory Manual, 3d ed. 2001, Chapter 12: DNA Sequencing. Thus, one of skill in the art would know how to determine the sequence of the at least one amplification product if there were no fluorescent indicator present in the first reaction composition. Applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

The Examiner rejects claim 49 under 35 U.S.C. §112, second paragraph as allegedly vague and indefinite for the recitation of "a 5'-nuclease fluorescent indicator." Office Action, page 2, section 2c. The Examiner states that the "specification describes the 5'-nuclease fluorescent indicator is a short oligonucleotide attached by fluorescent molecules and the fluorescent indicator is broken by the 5'nuclease activity of the DNA polymerase when it is replaced by the newly polymerized strand during PCR." Office Action, page 2, section 2c. Although the Examiner fails to mention that the fluorescent

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

molecule is quenched and does not fluoresce until it is broken by the nuclease activity of the DNA polymerase, the Examiner appears to clearly understand what a "5'-nuclease fluorescent indicator" is. Thus, the term "5'-nuclease fluorescent indicator" is clear.

The Examiner also states that "these limitations do not explicitly [describe] the fluorescent indicator itself but rather the process by which it is degraded." The Applicants respectfully disagree with the Examiner. The description of the process, including the fact that the 5'-fluorescent indicator is quenched (does not fluoresce) while it is still intact, describes the process by which the 5'-nuclease fluorescent indicator indicates the presence of a nucleic acid sequence. The Applicants fail to understand exactly how the definition of 5'-nuclease fluorescent is unclear, and request that the Examiner more specifically explain what is unclear about the term or its definition.

Further, even if, as the Examiner alleges, "these limitations do not explicitly [describe] the fluorescent indicator itself but rather the process by which it is degraded," this does not actually form a proper basis for rejection. Applicants would respectfully submit the question "so what?" If limitations describe a process which places clear requirements on the element of a claim, there is no indefiniteness. The Applicants respectfully request reconsideration and withdrawal of the §112, second paragraph rejection.

Further, if the Examiner still does not believe that claim 49 complies with 35 U.S.C. §112, second paragraph, because the Examiner has made clear that she understands what the Applicants are attempting to claim, the Applicants respectfully

FINNEGAN
HENDERSON
FARABOW
GARRETT &
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1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

request that the Examiner suggest an alternative language which would adequately describe the claimed invention in claim 49.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-25 and 68 under 35 U.S.C. §103(a) as allegedly obvious. Office Action, page 3, section 3. Specifically, the Examiner rejected claims 1-25 and 68 as allegedly obvious over Pritham et al., 1998, J. of Clinical Ligand Assay, Vol. (4):404-412 ("Pritham"), in view of Johnston-Dow et al., U.S. Pat. No. 6,103,465

The Examiner asserted that Pritham does not disclose the sequencing method used to detect a specific target nucleic acid as recited in the limitations of claim 1. *Id*, page 3. The Examiner also asserts that the "motivation is that the teachings of Pritham et al. indicate that fluorescent monitoring of PCR provides qualitative and quantitative information ... and the method of Johnston-Dow et al. applied the locus-specific nucleic acid amplification followed by sequence-specific detection of the amplified product for the DNA typing of HLA class I genes via DNA sequencing ...." *Id*, page 4.

However, the Examiner merely recited the qualities of the technologies disclosed in the references, but did not indicate where the references suggested a motivation to combine the references. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves ...." MPEP §2143.01. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id*, citing *In re Mills*, 916 F.2d

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The Examiner has not shown that either Pritham or Johnston-Dow suggest:

> "[a] method of determining the presence and sequence of at least one target polynucleotide in a sample comprising:
> combining nucleic acid from the sample with at least one reaction composition comprising a fluorescent indicator and amplification primers specific to the at least one target polynucleotide;
> amplifying the at least one target polynucleotide present in the reaction composition using the amplification primers to obtain at least one amplification product;
> irradiating the at least one amplification product such that the fluorescent indicator produces a fluorescent signal, wherein the intensity of the fluorescent signal is related to the quantity of the at least one amplification product;
> monitoring the amplifying by detecting the fluorescent signal from the fluorescent indicator;
> determining whether the at least one amplification product is present from the intensity of signal from the fluorescent indicator; and
> determining the sequence of the at least one amplification product if the at least one amplification product is present."

Thus, the Examiner has shown no suggestion or motivation to combine Pritham and Johnston-Dow, and has not made a case of *prima facie* obviousness.

The Examiner also rejected claims 26-50 as allegedly obvious over Pritham in view of Johnston-Dow and Wittwer et al., U.S. Pat. No. 6,174,670 ("Wittwer"). Office Action, page 5, section 4.

As stated in the arguments above, the Examiner has shown no motivation or suggestion to combine the teachings of Pritham and Johnston-Dow. The disclosure of Wittwer does not remedy these defects.

Applicants request reconsideration and withdrawal of the §103(a) rejections.

CONCLUSION

Applicants assert that pending claims 1-50 and 68 are allowable and request a timely issuance of a Notice of Allowance. In the event the Examiner does not find the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6676 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 11 , 2003

By: Robert W. Mann
Robert W. Mann
Reg. No. 48,555

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com